

Visceral Involvements and Long-term Sequelae in Drug-induced Hypersensitivity Syndrome

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KEYWORDS

- Drug-induced hypersensitivity syndrome
- Hepatitis • Limbic encephalitis • Renal dysfunction
- Sclerodermoid lesion • Systemic lupus erythematosus
- Type 1 diabetes mellitus • Thyroiditis

Drug-induced hypersensitivity syndrome (DIHS) is a life-threatening adverse systemic reaction characterized by skin rashes, fever, leukocytosis with eosinophilia and/or atypical lymphocytosis, lymph node enlargement, and liver and/or renal dysfunction.¹ The syndrome develops from 2 weeks to more than 6 weeks after initiation of a specific drug therapy. It has been estimated that DIHS occurs in 1 in 1000 to 1 in 10,000 exposures to antiepileptic drugs.² Previously, there was no consistent term for this phenomenon. Various terms had been used to refer to this syndrome using the generic names of the culprit drugs, such as phenytoin syndrome, allopurinol hypersensitivity syndrome, and dapson syndrome. Bocquet and colleagues³ proposed the name drug rash with eosinophilia and systemic symptoms (DRESS) to simplify the nomenclature for drug-hypersensitivity syndromes. Later, Descamps and colleagues⁴ and the Japanese Research Committee on Severe Cutaneous Adverse Reaction (J-SCAR) group^{5,6} showed a relationship between this drug reaction and human herpesvirus 6 (HHV-6) reactivation. Subsequently, the J-SCAR group coined the

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term DIHS to reflect its association with HHV-6.^{7,8} There is no significant difference in the clinical findings of patients who have been reported to have DRESS versus DIHS, although hypersensitivity reaction includes severe reactions with systemic symptoms without eosinophilia (eg, some hypersensitivity reactions following abacavir or allopurinol). Patients with this illness have a wide variety of complications involving multiple organs during the course of the disease, which persist long after resolution of the cutaneous eruptions, although the explanation for this multiorgan involvement remains unknown.

The severity of DIHS/DRESS is most frequently determined by the degree of visceral involvement. The mortality of DIHS/DRESS approaches 10%, primarily related to systemic involvement, including hepatitis, nephritis, myocarditis, and pneumonitis.⁹ This review focuses on the early and late complications observed in patients with DIHS/DRESS.

DIAGNOSIS AND CLINICAL COURSE OF DIHS/DRESS

DIHS/DRESS appears after a 2-week to 3-month exposure to a limited number of drugs, including anticonvulsants, dapsone, allopurinol, and minocycline.¹⁰ The delayed onset in relation to the introduction of the causative drug is 1 of the more important features of DIHS/DRESS. This feature can be used to distinguish DIHS/DRESS from other types of drug eruptions, which typically begin 1 to 2 weeks after initiating therapy.

The criteria for the diagnosis of DRESS proposed by Bocquet and colleagues³ are as follows: (1) cutaneous drug eruption; (2) hematologic abnormalities including eosinophilia greater than $1.5 \times 10^9/L$ or the presence of atypical lymphocytes; and (3) systemic involvement including adenopathy greater than 2 cm in diameter, hepatitis (liver transaminase values $>2 N$), interstitial nephritis, interstitial pneumonia, or carditis. These criteria emphasize 2 important characteristics: multiple organ involvement and eosinophilia.¹¹

The criteria for the diagnosis of DIHS established by J-SCAR⁸ are as follows: (1) maculopapular rash developing more than 3 weeks after starting a limited number of drugs; (2) prolonged clinical symptoms 2 weeks after discontinuation of the causative drug; (3) fever greater than $38^\circ C$; (4) liver abnormalities (eg, alanine aminotransferase [ALT] levels $>100 U/L$); (5) leukocyte abnormalities such as leukocytosis ($>11 \times 10^9/L$), atypical lymphocytosis ($>5\%$), and/or eosinophilia ($>1.5 \times 10^9/L$); (6) lymphadenopathy; and (7) HHV-6 reactivation. Diagnosis of typical DIHS requires the presence of all 7 criteria. An association between herpesvirus, particularly HHV-6, and DIHS has been increasingly reported; HHV-6 reactivation can be detected 2 to 4 weeks after the onset of this syndrome. Considering that HHV-6 reactivation is rarely detected in patients who develop a milder form of the disease, the detection of this viral reactivation is a useful marker for the diagnosis of DIHS/DRESS.^{7,12} The authors have recently shown that various herpesvirus reactivations, such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), and HHV-7, in addition to HHV-6, contribute to the internal organ involvement and the relapse of symptoms observed long after discontinuation of the causative drugs.¹³ In some patients with DIHS, sequential herpesvirus reactivations can be detected during the acute phase of DIHS, coincident with the various clinical symptoms. However, it is still a matter of debate to what extent herpesvirus reactivations are responsible for clinical symptoms and particularly exacerbations of symptoms like hepatitis.

Clinical features of this disease include the stepwise development of multiorgan failure and the frequent deterioration of clinical signs such as fever, skin rashes, and

liver or renal dysfunction, occurring even after discontinuation of the causative drug (Fig. 1). Fever usually precedes the skin rash by several days and is followed by a pruritic diffuse macular, sometimes reddish to lilac exanthema; some patients have a pustular eruption; occasionally the rash is maculopapular or erythema multiformelike. The patient's temperature ranges from 38 to 40°C, with temperature spikes that generate a concern for an underlying upper respiratory infection. The fever often persists for weeks. The maculopapular rash initially develops on the upper trunk and face, followed by involvement of lower extremities. Marked periorbital edema, a characteristic cutaneous manifestation of this syndrome, is frequently observed. The skin rash progresses to an exfoliative dermatitis or erythrodermic condition. Bilateral cervical, axillary, and inguinal lymphadenopathy, with tenderness, are commonly present. In many cases, these clinical features can be seen for weeks or months after cessation of the causative drug.¹⁴

Differentiation of DIHS from viral eruptions is the most challenging aspect of the diagnosis and care of patients afflicted with this disorder. Because the clinical presentation of DIHS/DRESS can resemble viral infections as well as autoimmune conditions, a careful drug history and physical examination are critical for making the correct diagnosis. Many of the patients are initially misdiagnosed with a viral illness, such as EBV or CMV-induced infectious mononucleosis or measles. However, these viral infections can be distinguished by the lack of eosinophilia and/or hypogammaglobulinemia. Kawasaki disease is more easily excluded by established diagnostic criteria and laboratory testing. Serum sicknesslike reaction can be distinguished by the presence of urticarial lesions and lack of internal organ involvement.¹⁵ Clinical manifestations of DIHS/DRESS can be indistinguishable from atopic erythroderma with a bacterial infection; however, hepatitis and/or nephritis are not commonly observed in an atopic condition. Pseudolymphomas have also been reported to develop in association with causative drugs such as phenytoin and carbamazepine.¹⁶ A diagnosis of

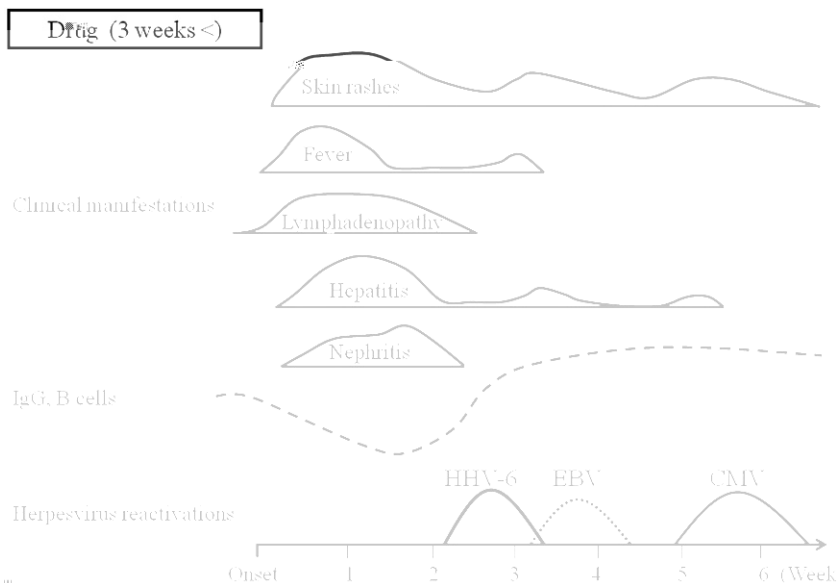


Fig. 1. Clinical symptoms and laboratory findings of DIHS/DRESS.

for rheumatoid arthritis with sulfasalazine. EBV DNA in this patient was detected in the serum during the course of DIHS/DRESS. It is therefore likely that herpesvirus reactivation may contribute to the appearance of HPS in patients with DIHS/DRESS.¹⁹

Hepatic Involvement

As reported, hepatitis is the most common organ dysfunction in DIHS/DRESS. Hepatomegaly accompanied by splenomegaly is frequently observed (Fig. 2). Liver abnormalities occur in up to 70% of patients and are characterized by a marked increase in serum ALT.^{20,21} The finding of an ALT level greater than 100 U/L is 1 of the criteria for DIHS established by J-SCAR.⁸ Increases in liver enzymes usually persist for several days after discontinuation of the offending drug. Prolonged prothrombin times and/or partial thromboplastin times are observed in severe cases.²² Severe hepatitis portends a prolonged course characterized by multiple exacerbations and remissions of the skin rash and the liver disease.²³ Among causative drugs, hepatitis is often observed in phenytoin-, minocycline-, or dapsone-induced DIHS/DRESS.¹⁰ Although most patients recover spontaneously, hepatic necrosis in the setting of coagulopathy and sepsis can cause death. The hepatitis is usually anicteric, but if it is icteric, it tends to have a poorer prognosis. Icterus is often observed in patients who have leprosy with dapsone-induced DIHS/DRESS. Cholangitis is rarely observed as a part of dapsone-induced DIHS/DRESS.²⁴ Liver involvement displays a mixed hepatocellular and cholestatic pattern. Results of hepatitis A, hepatitis B, and hepatitis C viral analyses are usually negative; however, underlying persistent viral infection, such as hepatitis B and hepatitis C virus infection, often causes a deterioration in liver function and prolongs liver dysfunction. According to the analysis of 62 cases by Tohyama and colleagues,²⁵ the flaring of symptoms such as fever and hepatitis was closely related to HHV-6 reactivation in patients with DIHS/DRESS. A patient reported by Eshki and colleagues²⁶ required a liver transplantation in an emergency setting; in this patient, a significant increase in anti-HHV-6 IgG antibody titers was detected in a serum sample collected several months before the transplantation. This case is important in that it confirmed that HHV-6 reactivation is a pretransplantation episode.

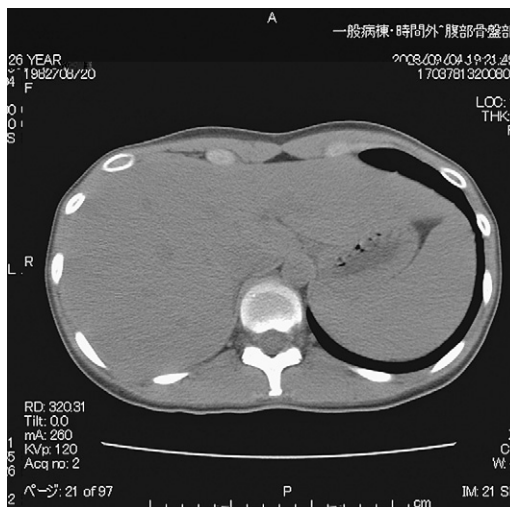


Fig. 2. Hepatomegaly in a patient with phenytoin-induced hypersensitivity syndrome showed by CT.

Fulminant hepatitis associated with DIHS/DRESS was reported in a patient who underwent intravenous intensive corticosteroid therapy, with a beneficial outcome.²⁷ A recent article has reported that fulminant liver failure after additional vancomycin treatment was observed in a patient with sulfasalazine-induced DIHS/DRESS.²⁸ Liver histology in this patient revealed infiltration of granzyme B⁺CD3⁺ lymphocytes close to apoptotic hepatocytes. This patient developed recurrent skin rashes, eosinophilia and moderate hepatitis after liver transplantation; HHV-6 DNA was not detected in the affected liver.

There are no strict guidelines for corticosteroid therapy in patients with hepatitis: In Europe, 1 mg/kg body weight/d of prednisolone is recommended, if ALT or aspartate aminotransferase values are more than 500 IU. Tapering is performed according to clinical course, whereby too early CS reduction tends to go along with transient exacerbations (liver enzymes, eosinophilia, and additional drug intolerance).

renal involvement

Renal involvement occurs in 11% of patients with DIHS/DRESS.²⁹ In the criteria for DIHS/DRESS, renal dysfunction can be substituted for liver abnormalities. Regarding multiple visceral involvement, renal involvement is particularly evident in allopurinol-induced DIHS/DRESS.¹⁰ In more than 80% of cases of allopurinol-induced DIHS/DRESS, patients showed evidence of renal impairment before commencing allopurinol. Because renal function declines steadily with age, elderly people are most vulnerable to developing this particular complication.³⁰ In many cases, laboratory studies show worsening renal insufficiency, ranging from a mild increase in serum creatinine levels to severe interstitial nephritis. In severe renal dysfunction, laboratory findings show high serum urea nitrogen and creatinine levels and low creatinine clearance. Urine analysis may reveal a substantial content of eosinophils. Kidney ultrasound examination is commonly normal and clinical symptoms are usually absent. A case of a patient with sulfasalazine-induced DIHS/DRESS who developed renal failure after corticosteroids withdrawal has been reported. Hemodialysis was shown to be effective in this patient.³¹ A kidney biopsy showed acute interstitial nephritis with an intense lymphocytic infiltrate and tubular necrosis.³² No specific deposits were detected by the immunofluorescence study. Accumulated case reports have shown that severe renal insufficiency increases the risk of mortality.

Pulmonary involvement

Although pulmonary involvement is rarely reported in DIHS/DRESS, interstitial pneumonia with eosinophilia is often observed in patients who have minocycline-induced DIHS/DRESS.¹⁰ It is possible that the cases with less severe pulmonary involvement are not reported, leading to a reporting bias with regard to the severity of the published cases.

Pulmonary complications include abnormal pulmonary function, acute interstitial pneumonitis, lymphocytic interstitial pneumonia, and acute respiratory distress syndrome (ARDS). Clinical symptoms such as a nonproductive cough and breathlessness are highly suggestive of pulmonary involvement. Pleuritis can also be observed during the course of DIHS/DRESS. Most patients with pulmonary involvement survive with no permanent sequelae; however, it may be life threatening in patients who show the characteristic findings of ARDS.³³

Lazoglu and colleagues³⁴ have reported a patient who developed Loeffler syndrome during the course of anticonvulsant hypersensitivity syndrome. Physical examination of this patient revealed marked rhonchi and increased fremitus in the lung fields. Chest

radiographs showed bilateral infiltrates and contrast-enhanced computed tomography (CT) of the chest revealed fluffy bilateral infiltrates. Abacavir-induced severe hypersensitivity reaction, occurring exclusively in genetically susceptible individuals (HLA-B5701*), also often shows some pulmonary involvement.^{35,36} Eosinophilia is often not present in these reactions, and the term DRESS therefore not used for abacavir-induced hypersensitivity reactions.

According to our and J-SCAR members' cases, it is likely that infectious pneumonia induced by *Pneumocystis jiroveci* or *Cryptococcus neoformans* could develop following the clinical resolution in patients with DIHS/DRESS.

Cardiac Involvement

Cardiac involvement is rarely observed during the course of the disease in patients with DIHS/DRESS. According to reports, myocarditis associated with DIHS/DRESS can develop at the onset of the disease or approximately 40 days after onset (Fig. 3).^{37,38} Clinically, symptoms suggestive of myocarditis include heart failure symptoms such as chest pain, unexpected tachycardia, breathlessness, and low blood pressure during the early course of DIHS/DRESS, although some patients are completely asymptomatic. Chest radiographs show cardiomegaly and pleural effusions and the electrocardiogram usually shows nonspecific ST-T changes, sinus tachycardia, or arrhythmias. The echocardiogram shows significant reduction in ejection fraction. Increases of serum cardiac enzymes, such as creatinine kinase and creatinine kinase MB-fraction, are detected but increased troponin-I levels are not seen.³⁹ Cardiac findings like these, especially if they are of recent onset in the presence of signs and symptoms of DIHS/DRESS, should be considered strongly suggestive of drug-induced myocarditis as part of DIHS/DRESS. Although endomyocardial biopsy remains the gold standard for the diagnosis of myocarditis, this is a highly invasive procedure that is not routinely performed.³⁸ Therefore, the diagnosis of myocarditis is still largely dependent on clinical suspicion rather than definitive diagnosis. In this setting, the final diagnosis of myocarditis is based on the presence of signs and symptoms of DIHS/DRESS, associated with recent onset of electrocardiogram changes, increased serum cardiac enzymes and a structurally normal heart and coronary arteries.^{38,40} Regardless of the cause, in patients with myocarditis and symptoms of heart failure, initial therapy should include besides corticosteroids (1 mg

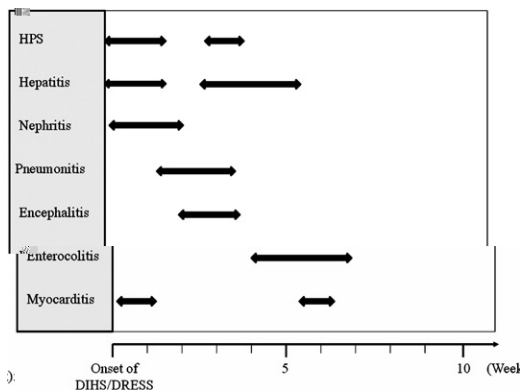


Fig. 3. Time interval between onset and visceral involvements during the course of DIHS/DRESS.

prednisolone/kg body weight/d), diuretics, an angiotensin-converting enzyme inhibitor and a β -blocker.⁴⁰

Recently, complete atrioventricular block-associated dapson-induced DIHS/DRESS has been reported. In this case, the atrioventricular block, as confirmed by electrocardiogram, was considered 1 of the multiple internal organ dysfunctions related to DIHS/DRESS, primarily because dyspnea, numbness of the limbs for several minutes, and sudden onset syncope were observed in conjunction with the onset of clinical signs and symptoms of DIHS/DRESS.⁴¹

Neurologic Involvement

Neurologic complications observed in DIHS/DRESS include meningitis and encephalitis. Meningoencephalitis develops approximately 2 to 4 weeks after the onset of this syndrome (see Fig. 3). The clinical features of this disease include coma, seizure, headache, and speech disturbance. Neurologic symptoms such as arm weakness and cranial nerve palsies are also observed. An electroencephalogram shows diffuse slow waves, with an occasional solitary spike, in the frontal and temporal leads without periodic patterns. A magnetic resonance imaging (MRI) scan of the brain shows bilateral lesions involving the amygdala, mesial temporal lobes, insula, and cingulate gyrus.⁴² The predilection for the hippocampal region in encephalitis is suggestive of limbic encephalitis. In accordance with the apparent fixed latency of HHV-6 reactivation after onset of DIHS/DRESS, the limbic encephalitis may be caused by reactivation of HHV-6 during the course of the disease. Masaki and colleagues⁴³ have reported a patient with allopurinol-induced DIHS/DRESS who developed encephalitis after reduction of systemic corticosteroids. Laboratory analysis showed an increase in anti-HHV-6 IgG titers and detection of HHV-6 DNA by means of polymerase chain reaction (PCR) assay in the cerebrospinal fluid (CSF). However, viral DNA cannot necessarily be detected in CSF samples obtained from patients with DIHS/DRESS after the onset of encephalitis.⁴⁴ These results may indicate secondary encephalitis or inappropriate timings of sampling. The progression of meningoencephalitis observed in DIHS/DRESS is similar to that observed in patients who have received a bone marrow transplant.

The authors have reported a case of SIADH, coincident with the clinical symptoms of limbic encephalitis, in a patient with DIHS/DRESS.⁴⁴ A similar unusual presentation of limbic encephalitis caused by HHV-6, associated with hyponatremia, has been previously described in several hematopoietic cell transplant recipients who developed graft-versus-host disease (GVHD). These 2 cases suggest that DIHS/DRESS and GVHD may have a common underlying condition, specifically reactivation of latent herpesvirus.^{45,46} Recent reports offer evidence that HHV-6 reactivation may underlie a characteristic limbic encephalitis syndrome following hematopoietic cell transplant; the cardinal features of this syndrome include memory loss, insomnia, electroencephalographic evidence of temporal lobe seizure activity, MRI signal intensity abnormalities of the temporal lobe, and SIADH.⁴⁷

Gastrointestinal Involvement

Abrupt gastrointestinal bleeding can be observed during the course of DIHS/DRESS. This is a life-threatening manifestation of the syndrome and is caused by CMV ulcers. CMV disease is a serious viral infection that occurs primarily in immunocompromised patients and rarely in immunocompetent patients. The gastrointestinal ulcers can be misdiagnosed as steroid-induced gastric ulcers in these patients unless special attention is given to the possibility of CMV disease. Endoscopic examination reveals arterial bleeding from punched-out gastric ulcerations.⁴⁸ Because of the high mortality

associated with these ulcerations, early intervention with emergency endoscopic clipping and blood transfusion is usually required.

The gastrointestinal manifestation often appears concomitantly with cutaneous CMV ulcers on the shoulders and trunk. Biopsy specimens obtained from the gastric mucosa and the skin show cytomegalic cells with the characteristic owl's eye intranuclear inclusions in the infiltrating cells. The CMV infection is usually confirmed by immunohistochemical analysis using anti-CMV monoclonal antibody.⁴⁸ Autopsy results obtained from a patient with severe DIHS/DRESS revealed disseminated CMV infection involving the lung, myocardium, kidney, adrenal gland, liver, pancreas, spleen, and skin.⁴⁹

Although it is uncommon to suspect CMV reactivation during the disease, the presence of scratch dermatitis and erythematous rashes, unexplained slight fever, and lumbar pain are considered as symptoms suggestive of the development of gastrointestinal CMV disease. In addition, a reduction in platelet and white blood cell counts and a decreased serum globulin level are also useful markers predictive of CMV reactivation. To detect CMV reactivation, examination of CMV antigenemia in the peripheral blood is the most useful diagnostic tool because this is not a time-consuming technique.

CMV reactivation occurs in a predictable time course during the course of DIHS/DRESS. In most patients, CMV DNA is detected during a 4- to 5-week period after the onset of disease (see Fig. 3), regardless of the administration of systemic corticosteroids, at approximately 10 days to 3 weeks after HHV-6 reactivation.^{48,50} Although comprehensive explanations are unavailable, several preexisting factors that contribute to CMV reactivation are reported in retrospective studies. The results indicate that elderly patients, particularly those older than 60 years, and male patients with antecedent high HHV-6 DNA loads are at risk for overt CMV disease.⁴⁸

If CMV antigenemia is positive in patients with DIHS/DRESS, treatment with the antiviral agent ganciclovir is recommended until CMV antigenemia becomes negative.

Involvement of Other Organ Systems

A patient with anticonvulsant hypersensitivity syndrome developed enlargement of the parotid glands with cervical lymphadenopathy in the acute stage.³⁴ Descamps and colleagues documented a patient with DIHS/DRESS who showed pancreatitis and increased serum amylase and lipase levels. Herpes labialis and herpes zoster are also observed in patients with DIHS/DRESS.^{13,20} The former is often recognized as an epiphenomenon of the disease, whereas the latter may precede the onset of this disease. These herpetic cutaneous lesions should be considered as a reactivation event in the sequential reactivations of herpesviruses occurring in patients with DIHS/DRESS.

LONG-TERM SEQUELAE OBSERVED AFTER SYMPTOM-FREE INTERVAL IN DIHS

Several articles, including the authors', have shown the occurrence of autoimmune diseases and/or production of autoantibodies after resolution of DIHS/DRESS (Box 2). These autoimmune diseases include type 1 diabetes mellitus (DM),⁵¹⁻⁵⁶ autoimmune thyroid disease,^{38,56} sclerodermoid GVHD-like lesions,⁵⁷ and lupus erythematosus^{58,59} (Fig. 4). Some of these autoimmune diseases are similar to those seen after bone marrow transplantation. According to the reports, autoimmune diseases have developed from several months to years after the apparent clinical resolution of DIHS/DRESS. Because of the long symptom-free interval, it is difficult to establish an association between DIHS/DRESS and autoimmune diseases. The association

Box 2
Visceral organ involvements in late stage
Bullous pemphigoid (BP)
Enteropathy
Sclerodermoid lesions
Systemic lupus erythematosus
Type 1 DM
Thyroiditis

between DIHS/DRESS and these autoimmune diseases is overlooked unless physicians pay special attention to the previous history of DIHS/DRESS and the presence of viral reactivations that trigger the development of autoimmune diseases.

type1 M

In rare cases, fulminant type 1 DM may develop in association with DIHS/DRESS. Type 1 DM is classified into classic autoimmune type 1A DM and idiopathic type 1B DM. Diagnosis of type 1 DM is confirmed by low levels of serum C-peptide. Fulminant type 1 DM has been recently characterized by its rapid onset with an absence of diabetes-related autoantibodies. In type 1 DM diabetes-related autoantibodies, such as antiglutamic acid decarboxylase (GAD) and islet cell antibodies, are usually not detected, indicating that b-cell failure is not of autoimmune origin.^{51,52,60} Initial clinical manifestations of fulminant type 1 DM reveal vomiting and dull epigastric pain. Laboratory findings show hyperglycemia, hyperosmolarity, and metabolic acidosis. These findings are compatible with diabetic ketoacidosis. Increases of pancreatic exocrine enzyme levels such as lipase and amylase are observed during the course of the disease, consistent with acute pancreatitis.⁵³ De novo onset type 1 DM appears around 3 weeks and 10 months after the onset of the clinical symptoms of DIHS/DRESS^{51–54,60} (see Fig. 4); type 1 DM develops during corticosteroid treatment of DIHS/DRESS in most patients. Early detection and intervention for this serious complication should be given to patients with DIHS/DRESS. The cause of this particular appearance of type 1 DM remains unknown. Based on previous reports implicating viral agents such as enteroviruses, rubella, mumps, and CMV in the potential triggers,⁶¹ it seems likely that herpesvirus reactivation could contribute to the development of the type 1 DM in patients with DIHS/DRESS. In addition,

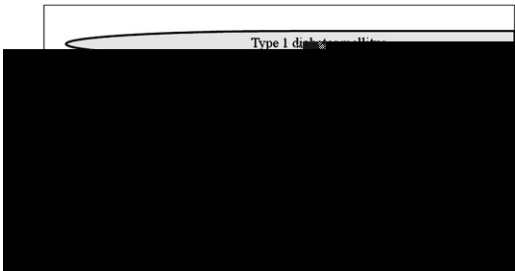


Fig. 4. Autoimmune diseases after clinical resolution of DIHS/DRESS. SLE, systemic lupus erythematosus.

because analyses of HLA antigens showed that DQA1*0303 and DQB1*0401 are associated with fulminant type 1 DM, DIHS/DRESS may have triggered the fulminant type 1 DM in this particular group.⁶²

On the other hand, in autoimmune type 1 DM, various autoantibodies including IA₂, anti-GAD, are detected. Autoimmune type 1 DM is not common in patients with DIHS/DRESS. The coexistence of autoimmune type 1 DM and Graves disease has been observed in relation to DIHS/DRESS. In a reported case, 4 months after the diagnosis of DIHS/DRESS, manifestations of type 1 DM developed; low anti-GAD antibody titers are detected.⁵⁵ In addition, Brown and colleagues⁵⁶ have recently reported a case of a patient with minocycline-induced DIHS/DRESS who developed autoimmune hyperthyroidism, type 1 DM, and additional serologic findings suggestive of evolving systemic autoimmunity. In this case, clinical manifestations of autoimmune type 1 DM developed 7 months after discontinuation of the causative drug (see Fig. 4); various autoantibodies including IA₂, anti-GAD, -thyroid peroxidase (TPO), -thyroglobulin, -nuclear, and -SSA antibodies were also detected during this period; HLA antigen typing revealed DQA1*0303. Such findings arouse suspicion of the development of autoimmune diseases like polyglandular autoimmune syndrome in patients with DIHS/DRESS.⁶³

After the diagnosis of type 1 DM, prompt insulin injection therapy should be commenced. When the diagnosis is overlooked, consequences can be life threatening.

hyroid dysfunction hyroiditis

In some patients with DIHS/DRESS, endocrinologic evaluation reveals various thyroid gland abnormalities, such as increased free thyroxine (T₄), low thyroid-stimulating hormone (TSH), and increased TSH levels. These abnormal findings may escape detection if thyroid markers are not evaluated. Levothyroxine replacement therapy may be required for hypothyroidism. Of those patients who show thyroid dysfunction, some may later develop autoimmune thyroid disease.

Graves disease could also develop after the resolution of DIHS/DRESS. The interval between the discontinuation of the causative drug and the onset of Graves disease is approximately 2 to 4 months. According to Brown and colleagues,⁵⁶ at first low TSH and high free thyroxine (FT₄) levels and markedly increased antithyroglobulin and anti-TPO antibody titers are detected without any symptoms; anti-TSH receptor antibodies are negative. Markers of Graves disease are also negative, and a diagnosis of autoimmune thyroiditis in the thyrotoxic phase is usually made.⁵⁶ Approximately 5 months after cessation of the causative drug, the patient develops clinical symptoms such as palpitation, irritability, and difficulty sleeping with laboratory findings compatible with Graves disease (see Fig. 4). Thyrotoxicosis was also observed as the presenting symptom in a patient with dapsone-induced DIHS/DRESS.³⁸

On the other hand, Hashimoto disease, revealing anti-TPO and antithyroglobulin antibodies, is also observed after the resolution of clinical symptoms of DIHS/DRESS. The authors have experienced a patient with increased anti-TPO antibodies and antithyroglobulin antibodies during the course of DIHS/DRESS with multiple herpesvirus reactivations such as HHV-6, EBV, HHV-7, and CMV. The patient developed Hashimoto disease 3 years after resolution of the clinical symptoms of the disease with a significant increase in anti-TPO and antithyroglobulin, and goiter.

According to our analyses, approximately 3 months to 1 year after resolution of DIHS/DRESS, antithyroid antibodies are detected in our patients with DIHS/DRESS without any clinical manifestations. Therefore, we examined several autoantibody titers, including antinuclear antibody (ANA) titer, anti-TPO antibodies, and

antithyroglobulin antibodies at the acute stage as well as up to 1 year after resolution of DIHS/DRESS. Our analyses showed that anti-TPO and antithyroglobulin antibodies increased in some patients without any clinical symptoms or functional alterations of the thyroid gland (T. Ishida, unpublished data, 2010).

Sclerodermoid Lesions

The authors have reported a patient who developed systemic sclerosis-like lesions 3 to 4 years after zonisamide-induced DIHS/DRESS⁵⁷ (see Fig. 4). The patient presented with multiple brownish, indurated plaques with xerosis on the extremities. In this patient, a wide variety of manifestations were observed, including pancytopenia, diffuse alopecia, thyroid dysfunction, and sclerodermoid lesions, with an increase in various autoantibody titers. The patient's past history revealed that fever, liver dysfunction, and skin rashes had occurred along with HHV-6 reactivation, which fulfilled the criteria for DIHS/DRESS. ANA and rheumatoid factor were negative during the course of DIHS/DRESS but became detectable with the appearance of diffuse alopecia. A dramatic increase in ANA was found at the initial presentation to our department because of sclerodermoid GVHD-like lesions, indicating that the disease process of DIHS/DRESS may act as a trigger for the development of autoimmune disease.^{57,58} Autoimmune-like lesions resembling scleroderma or lupus erythematosus often develop as manifestations of chronic GVHD after organ transplantation. Generalized sclerodermatous lesions appeared between days 332 and 876 in a group of patients, after donor leukocyte infusion, in this setting.⁶⁴ Autoimmune reactions ranging from thyroid dysfunction to sclerodermoid GVHD-like lesions appeared 1 to 4 years after the onset of DIHS/DRESS in this patient, a time frame similar to that of chronic GVHD.

Systemic Lupus Erythematosus

A patient who developed systemic lupus erythematosus after resolution of carbamazepine-induced DIHS/DRESS with reactivation of HHV-6 and EBV has been reported.^{58,59} After resolution of DIHS/DRESS, the patient remained asymptomatic for 4 years until he presented with cervical lymphadenopathy and erythematous lesions on the face and chest. Clinical manifestations and histology of his lymphadenopathy were consistent with a diagnosis of Kikuchi-Fujimoto disease. One week later, his erythematous lesions deteriorated, evolving into the typical lesions of lupus erythematosus on the face, chest, and back (Fig. 5). Laboratory findings showed leukopenia, positive ANA, and decreased serum C3 and C4 levels. Histologic examination of the erythematous lesion showed vacuolar changes of basal cell layer with a moderate lymphocytic infiltration around follicles and sweat glands. The lupus band test of the skin lesion was positive and lupus nephritis was confirmed by renal biopsy. Expression of EBV-encoded RNA was detected in the lymph node by in situ hybridization. The presence of EBV DNA was also confirmed by PCR in the lymph node.⁵⁹ EBV reactivations in this patient may have been involved in the pathogenesis of systemic lupus erythematosus after Kikuchi-Fujimoto disease. These findings could be interpreted as an indication that herpesvirus reactivation and/or the immune response to them can occur during the disease process of DIHS/DRESS and may render refractory individuals susceptible to autoimmune disease.

Autoimmune Bullous Diseases

Autoimmune bullous disease and autoantibodies rarely appear after the onset of DIHS/DRESS. Kijima and colleagues⁶⁵ have reported a case of a patient who developed recalcitrant bullous lesions on the trunk and extremities 77 days after the onset of symptoms,

with an increase in peripheral eosinophil counts during treatment with systemic cortico-

erythematosus develop after a disease-free interval of several years. The immune dysfunction in DIHS/DRESS may serve as an excellent tool for investigating the pathogenesis of autoimmune diseases occurring after viral infections. To identify patients at risk for developing autoimmune diseases, thereby improving overall patient management, patients with DIHS/DRESS, in particular those with symptoms suggestive of viral reactivation, should be carefully followed up even after resolution of clinical symptoms. Studies of DIHS/DRESS may provide further insight into the pathogenesis of visceral organ diseases.

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